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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/699,394	DRABORG ET AL.	
	Examiner	Art Unit	
	WILLIAM W. MOORE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18-47 and 49-56* is/are pending in the application.

4a) Of the above claim(s) *49 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-47,50-54 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20081013*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 13 October 2008 has been entered, canceling claim 17 and amending claims 16, 18-47, and 56. Claims 1-15 and 48 having previously been canceled, claims 16, 18-47 and 50-56 remain in the application, of which claim 55 remains withdrawn from consideration as drawn to a non-elected invention where it requires no amino acid insertion, deletion or substitution at the subtilisin BPN'-correspondent position 62 according to claim 16, from which it depends. It is noted that claim 55 thus improperly depends from claim 16. The amendments introduce no new matter and remove the bases for rejections of record under 35 U.S.C. § 103 that had combined the disclosures of Brode et al. with teachings of any of Ness et al., Fanø et al., Weisgerber et al., Christianson et al., '735, and Bott et al., which rejections are now WITHDRAWN. The convention retained during the prosecution history of this application of representing subtilisin BPN' positions in parentheses, while setting forth the corresponding positions in amino acid sequences of other group I-S1, and group I-S2, subtilisins in brackets, is maintained in rejections hereinbelow.

Claim Objections

Claim 16 is objected to because of the following informalities: (1) A comma, rather than an amino acid substituent, immediately follows the position number 61 where the claim is intended to indicate substitutions at a position 61. (2) Two commas, rather than a single comma, follow the "S" in the substitution V203S. Appropriate correction is required, i.e., amending the claims to instead state "G61R,GP," and, with reference to claim 39, "V203S,F,". In the event that the absence of "S" – serine – is inadvertent in claim 39, which describes only "V203F", claim 39 is included together with claim 16 in the following rejection under 35 U.S.C. § 102.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16, 18, 32, 39 and 51-54 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brode et al. US 6,599,730, of record.

Brode et al. '730 disclose preparation of variant subtilisins 309, a group I-S2 subtilase, that comprise many different sets of multiple amino acid substitutions, including both of the substitution sets **N**(62)[61]**S/Q/D/E/P+P**(129)[128]**N/E** and **N**(62)[61]**S/Q/D/E/P+V**(203)[197]**S** according to claims 16, 18, 32, 39, 51, and 52 herein. See cols. 3, 5, 6, 7-10, and Tables 3-6 and 33-37 at cols. 16-18 and 67-96 of Brode et al., '730. Brode et al. '730 also disclose that the multiply-substituted subtilisins 309 are advantageously formulated in detergent compositions to provide improved wash performance due to their "decreased absorption to, and increased hydrolysis of, an insoluble substrate" when used methods of cleaning textiles or surfaces, wherein detergent compositions further comprise a surfactant and other enzymes, including "cellulases, lipases, amylases and [other] proteases", meeting the limitations of claims 53 and 54 herein. See the abstract and cols. 96-99, particularly col. 98, at lines 42-47.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

A. Claims 16, 18, 37 and 51-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brode et al. US 6,599,730, discussed above, in view of van Eekelen et al., **US 5,336,611**, and Mulleners et al. **US 6,287,841,** both made of record herewith.

The teachings of Brode et al. '730, discussed above, are taken as before.

Van Eekelen et al. teach the preparation of variant subtilisins PB92, a group I-S2 subtilase, that comprise sets of multiple amino acid substitutions, including **M**(175)[169]**I** and **M**(175)[169]**S** substitutions. See col. 9, lines 22-28, in view of col. 8, lines 43-46, where van Eekelen et al. teach that neutral substituents for M169 comprise "A, L, I, V, S" and "T", as well as col. 10, at line 16, and items 21, 23, and 30 in the Table of Example 12 at col. 24 of van Eekelen et al. van Eekelen et al. further teach the incorporation of their variant I-S2 subtilases in detergent compositions at cols. 15-25.

Mulleners et al. similarly teach the preparation of variant subtilisins PB92, and extend their teaching to variant subtilisins 309, having amino acid substitutions at position 169 numbered according to the amino acid sequences of both subtilisins PB92 and 309. See col. 3, at lines 5-23, col. 5, at line 63, the paragraph spanning cols. 6 and 7, col. 7, at lines 18-19, col. 11, at about line 38, and, in particular, claim 3, where a substitution at position (175)[169] in either of the group I-S2 subtilases may be combined with an amino acid substitution at position (62)[60]. Mulleners et al. similarly teach the incorporation of their variant I-S2 subtilases in detergent compositions at cols. 8-14, where such detergent compositions may further comprise "an amylase, cellulase, or lipase" as taught at lines 25-26 of col. 8.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a variant group I-S2 subtilase, including a variant subtilisin 309, that comprises any of the **N**(62)[61]**S**/**Q**/**D**/**E**/**P** substitutions that Brode et al. teach will improve wash performance together with a substitution of alanine(A), leucine(L), isoleucine(I), valine(V), serine(S) or threonine(T) for a methionine present at the subtilisin BPN'-correspondent position 175, which is position 169 in the amino acid sequences of the group I-S2 subtilisins 309 and PB92, as taught by van Eekelen et al. and Mulleners et al. and to prepare a detergent composition comprising such variant subtilases, as well as cellulases, lipases, and amylases, according to claims 16, 18, 37 and 51-54 herein. This is because Brode et al. teach that each wash performance-improving amino acid substitution, such as any of the **N**(62)[61]**S**/**Q**/**D**/**E**/**P** substitutions, may be combined with other amino acid substitutions elsewhere in an I-S2 subtilase and because each of van Eekelen et al. and Mulleners et al. teach that it is advantageous to incorporate group I-S2 subtilases improved by multiple amino acid substitutions that, according to van Eekelen et al. include replacing the methionine present at the subtilisin BPN'-correspondent position 175, which is position 169 in the amino acid sequences of the group I-S2 subtilisins 309 and PB92 with any of A, L, I, V, S, or T, and each of Brode et al., van Eekelen et al., and Mulleners et al. teach that such variant subtilases may be incorporated in detergent compositions that Brode et al. and Mulleners et al. teach may also

comprise other enzymes such as cellulases, lipases, and amylases. Such an artisan would have had a reasonable expectation of success in preparing such subtilisin 309 or PB92 variants having improved wash performance and preparing detergent compositions that comprise such variants and other enzymes, according to claims 16, 18, 37 and 51-54 herein, because the amino acid substitutions of Brode et al. are all at solvent-exposed positions of a subtilisin and the amino acid substitutions of van Eekelen et al. and Mulleners et al. are readily combined with other substitutions, which according Mulleners et al. include, see claim 3, amino acid substitutions at the subtilisin BPN'-correspondent position 62. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

B. Claims 16, 18, 19, 47, and 50-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any of Brode et al. US 6,436,690, US 6,455,295, US 6,475,765, or US 6,599,730, all of record, in view of Bryan et al. **US 5,567,601**, made of record herewith.

The teachings of Brode et al. '730, discussed above, are taken as before.

Like Brode et al. '730, each of Brode et al. '690, '295, and '765 teach the preparation of variant group I-S1 subtilases – respectively, subtilisin BPN', subtilisin Carlsberg, and subtilisin DY – whereas the variant subtilisin 309 of Brode et al. '730 is a group I-S2 subtilase, comprising sets of multiple amino acid substitutions, where each of Brode et al. agree that any of the **N**(62)[61]**S/Q/D/E/P** substitutions are advantageously combined with other amino acid substitutions in group I-S1 and I-S2 subtilases, where such substitutions improve wash performance of the variant, relative to the native subtilase, in a wash liquor.

Bryan et al. teach the preparation of variant subtilases – including the various group I-S1 and group I-S2 subtilases wherein Brode et al. '690, '295, '730, and '765 teach multiple amino acid substitutions – that comprise the thermodynamically stabilizing amino acid substitution **Q2L** according to claims 16 and 19 herein. See the paragraph spanning cols. 1 and 2, the second paragraph of col. 5, and claims 1, 2, 7, 8, 10, and 11, of Bryan et al. Bryan et al. also teach that their variant subtilases are advantageously prepared for use "in environments containing high concentrations of metal chelators" that compromise the stability of subtilisins. See col. 3, lines 41-46.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a variant subtilase comprising any of the substitutions **N**(62)[61]**S/Q/D/E/P** taught to improve wash performance in each of the four patents to Brode et a. relied on herein

together with the amino acid substitution **Q2L** that Bryan et al. teach is thermodynamically stabilizing and to prepare a detergent composition comprising such variant subtilases, as well as cellulases, lipases, and amylases, according to claims 16, 18, 19, 47, and 50-54 herein. This is because (1) Bryan et al. teach that a **Q2L** substitution yields a variant subtilase stabilized for use in environments containing high concentrations of metal chelators that may compromise the stability of subtilases and such an artisan, in view of the body of prior art of record herein, would recognize that detergent compositions often contain chelators producing such environments in a wash liquor, (2) each of Brode et al. teach that each wash performance-improving amino acid substitution may be combined with other amino acid substitutions elsewhere in I-S1 and I-S2 subtilases, and (3) each of Brode et al. teach that it is advantageous to incorporate subtilases improved by multiple amino acid substitutions in detergent compositions that also comprise other enzymes such as cellulases, lipases, and amylases. Such an artisan would have had a reasonable expectation of success in preparing a subtilisin variant, whether of group I-S1 or group I-S2, having improved thermal stability and improved wash performance when combining an **N**(62)[61]**S/Q/D/E/P** substitution of any of Brode et al. with the **Q**(2)[2]**L** substitution of Bryan et al. as well as preparing detergent compositions comprising such variants and other enzymes, according to claims 16, 18, 19, 47, and 50-54 herein, because the amino acid substitutions of Brode et al. are all at solvent-exposed positions of a subtilisin and the amino acid substitution of Bryan et al. occurs adjacent to the amino terminus of an I-S1 or I-S2. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

C. Claims 16, 18, 43, and 51-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brode et al., US 6,436,690, US 6,455,295, US 6,475,765, or US 6,599,730, all of record, and Christianson et al., **US 5,500,364,** made of record herewith.

Teachings of Brode et al. '765, '690, '295, or '730, discussed above, are taken as before.

Christianson et al. '364 teach the preparation of variants of a group I-S2 subtilase, the *Bacillus lentus* DSM 5483 protease, comprising the substitution **S**(242)[236]**T**, according to claims 16, 43 and 51 herein. See Tables 2 and 3 at cols. 8-10, and claims 1 and 8. Christianson et al. '364 teach that this is among the amino acid substitutions advantageously introduced in a subtilase amino acid sequence for structural stabilization, primarily by enhancing interior van der Waals interactions, thereby increasing shelf stability and sustaining its catalytic

activity in detergent compositions. See col. 1, at lines 40-56, and col. 19, line 22, through col. 20, line 24.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare subtilase variant comprising any of the substitutions **N**(62)[61]**S/Q/D/E/P** that each of the four patents to Brode et al. relied upon herein teach will improve wash performance together with the structurally stabilizing **S**(242)[236]**T** substitution taught by Christianson et al. '364 where the parent subtilase is either a group I-S2 subtilase, such as subtilisin 309, as well as to prepare a detergent composition comprising such a variant subtilase as well as cellulases, lipases, and amylases. This is because Christianson et al. '364 teach that their substitutions provide improved, stable variant subtilases useful in detergent compositions and because Brode et al. teach that it is advantageous to make **N**(62)[61]**S/Q/D/E/P** substitutions in both group I-S1 and I-S2 subtilases to improve their wash performance and the incorporation of such variant subtilases with further enzymes, such as cellulases, lipases, and amylases, in a detergent composition. Such an artisan would have had a reasonable expectation of success in preparing a subtilisin variant, whether of group I-S1 or group I-S2, having improved wash performance as well as an increased shelf stability and retained catalytic activity in detergent compositions when combining an **N**(62)[61]**S/Q/D/E/P** substitution of any of Brode et al. with the **S**(242)[236]**T** substitution of Christianson et al. '364 as well as preparing detergent compositions comprising such a variant and other enzymes, according to claims 16, 18, 43, and 51-54 herein, because the amino acid substitutions of Brode et al. are all at solvent-exposed positions of a subtilisin, the amino acid substitutions of Christianson et al. '364 are primarily made at positions at the internal surfaces of a group I-S2 subtilase. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

D. Claims 16, 18, 21-24, 26, 27, 31, 41, 45-47, 51-54, and 56 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any among Brode et al. US 6,436,690, US 6,455,295, US 6,475,765, or US 6,599,730, and Ghosh et al. **US 6,376,450**, made of record herewith.

The teachings of Brode et al. '765, '690, '295, or '730, discussed above, are taken as before.

Ghosh et al. '450 teach the preparation of multiply-substituted variant subtilisins 309, a group I-S2 subtilase, comprising the amino acid substitutions **A13V, R19L, S24P, T38S, G61R, S78T, M199I, A228T, Y263H, Y263F,** and **S265G** where each of these positions, while present in a group I-S2 subtilase, is expressly numbered by Ghosh et al. '450 according to its

correspondence with the amino acid sequence of subtilisin BPN'. See Tables II, V, VII, and X. Ghosh et al. '450 further teach that the variant group I-S2 subtilases comprising one or more of these substitutions are advantageously added, together with other enzymes including lipases, amylases, cellulases, and other proteases, to cleaning compositions, including detergent compositions, to "provid[e] improved and enhanced cleaning of fabrics, dishware, tableware, kitchenware, cookware, and other hard surface substrates". See col. 4, lines 45-53, and col. 65, line 1, through col. 108, line 50.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a subtilisin variant comprising any of the **N**(62)[61]**S/Q/D/E/P** substitutions that each of the four patents to Brode et al. relied on herein teach will improve wash performance in subtilases, including a group I-S2 subtilase such as subtilisin 309, and to further introduce one or more of the **A13V, R19L, S24P, T38S, G61R, S78T, M199I, A228T, Y263H, Y263F,** and **S265G** amino acid substitutions taught by Ghosh et al. '450 to be advantageous in a variant group I-S2 subtilisin according to claims 16, 18, 21-24, 26, 27, 31, 41, 45-47, 51, 52, and 56 herein, and obvious as well to prepare a detergent composition comprising such a variant subtilisin and other enzymes of claims 53 and 54 herein. This is because each of Brode et al. teach the advantages of the **N**(62)[61]**S/Q/D/E/P** substitutions in improving wash performance, because Ghosh et al. '450 teach that each of their many amino acid substitutions are both individually advantageous as well as advantageously combined with one or more further amino acid substitutions in a subtilase for use in detergent compositions at the time the invention was made. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

E. Claims 16, 18, 20, 22, 46, and 50-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any among Brode et al. US 6,436,690, US 6,455,295, US 6,475,765, or US 6,599,730, and von der Osten et al. US 6,245,901, all of record.

The teachings of Brode et al. '765, '690, '295, or '730 discussed above, are taken as before.

Von der Osten et al. '901 teach the preparation variants of both group I-S1 subtilases and group I-S2 subtilases, including subtilisin 309, comprising one or more of the amino acid substitutions **R**(10)[10]**K**, **R**(19)[19]**K**, or **N**(269)[263]**K**, as well as incorporation of the subtilase variants in detergent compositions, according to claims 16, 18, 20, 22, 46, and 50-54 herein. See col. 9, lines 33-44, col. 20, lines 40-56, and col. 44, lines 13-32. While von der Osten et al.

'901 further teach the subsequent covalent modification of lysine substituents at these positions to reduce the immunogenicity of the subtilisin; the present claims require no more than a substitution of lysine at these positions.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a group I-S1 subtilase or group I-S2 subtilase variant comprising any of the **R**(10)[10]**K**, **R**(19)[19]**K**, or **N**(269)[263]**K** substitutions taught by von der Osten et al. '901, in order to provide a basis for reducing immunogenicity of the subtilase, and that further comprises one of the **N**(62)[61]**S/Q/D/E/P** substitutions that each of the four patents to Brode et al. relied on herein teach will improve wash performance, as well as to prepare a detergent composition comprising such a variant subtilase as well as cellulases, lipases, and amylases. This is because von der Osten et al. '901 teach that lysine substitutions are prerequisites for decreasing the immunogenicity of this common subtilase component of detergent compositions and each of Brode et al. teach that incorporating further enzymes in detergent compositions is advantageous. Such an artisan would have had a reasonable expectation of success in preparing a subtilisin variant having decreased immunogenicity due to introducing one or more of the **R**(10)[10]**K**, **R**(19)[19]**K**, or **N**(269)[263]**K** substitutions taught by von der Osten et al. '901, in view of the further modifications taught by von der Osten et al. '901, as well as an increased shelf stability and retained catalytic activity in detergent compositions when combining an **N**(62)[61]**S/Q/D/E/P** substitution of any of Brode et al. and in preparing detergent compositions comprising such variants and other enzymes, according to claims 16, 18, 20, 22, 46 and 50-54 herein. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

F. Claims 16, 18, 33, and 50-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any among Brode et al. US 6,436,690, US 6,455,295, US 6,475,765, or US 6,599,730, and von der Osten et al. **US 6,300,116**, made of record herewith.

The teachings of Brode et al. '765, '690, '295, or '730 discussed above, are taken as before.

Von der Osten et al. '116 teach the preparation variants of both group I-S1 subtilases and group I-S2 subtilases, including subtilisin 309, comprising one or more of the amino acid substitutions **T**(134)[132]**A** or **Y**(171)[169]**C** that reduce the autoproteolysis of subtilases in solutions, such as wash liquor, rendering the variant subtilases more stable components of detergent compositions, which compositions may also comprise other "protease[s], a lipase, an

amylase, and/or a cellulase". See col. 6, lines 18-63, from col. 16, at line 62, through col. 17, at line 54, and col. 33, at lines 27-29.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a group I-S1 subtilase or group I-S2 subtilase variant comprising either of the **T**(134)[132]**A** or **Y**(171)[169]**C** substitutions that von der Osten et al. '116 teach will prolong the shelf life and proteolytic activity of both group I-S1 subtilases and group I-S2 subtilases with one of the **N**(62)[61]**S/Q/D/E/P** substitutions that each of the four patents to Brode et al. relied on herein teach will improve wash performance, as well as to prepare a detergent composition comprising such a variant subtilase as well as cellulases, lipases, and amylases. This is because von der Osten et al. '116 teach that their substitutions provide more stable subtilases as components of detergent compositions, each of Brode et al. teach that their amino acid substitutions provide subtilases with improved wash performance and both von der Osten '116 and each of Brode et al. teach that incorporating further enzymes in detergent compositions is advantageous. Such an artisan would have had a reasonable expectation of success in preparing a subtilisin variant having improved stability due to introduction of either of the **T**(134)[132]**A** or **Y**(171)[169]**C** substitutions taught by von der Osten et al. '116 as well as improved wash performance in detergent compositions when combining an **N**(62)[61]**S/Q/D/E/P** substitution of any of Brode et al. and in preparing detergent compositions comprising such variants and other enzymes, according to claims 16, 18, 33, and 50-54 herein. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

G. Claims 16, 18, 24, 29, 46, and 50-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any among Brode et al. US 6,436,690, US 6,455,295, US 6,475,765, or US 6,599,730, discussed above, in view of Poulose et al., **US 7,306,937**, made of record herewith.

The teachings of Brode et al. '765, '690, '295, or '730, discussed above, are taken as before.

Poulose et al. '937 are available as prior art under 35 U.S.C. § 102(a) in view of the teachings of the preparation of both group I-S1 and I-S2 subtilases having modified net charge comprising the amino acid substitutions **R**(45)[44]**H**, **K**(94)[92]**N**, and **E**(271)[265]**A** at page 16 of their 16 January 2002-filed US priority application No. 60/350,222. Poulose et al. '937 teach that these substitutions shift the isoelectric point of a variant subtilase relative to an unmodified subtilase to better adapt the variants, and maintain their bulk properties upon incorporation in

detergent compositions that produce diverse pH ranges when dissolved in wash liquor. See the discussion at cols. 7-9, the list of preferred charge-altering substitutions at col. 10, lines 33, 36, and 57, and Figures 3A and 3B. Poulose et al. '937 also teach that the detergent compositions wherein their net charge-modified variants are incorporated may also comprise other proteases, amylases, cellulases, lipases, and endoglycosidases. See col. 20 at lines 62-65. See col. 4, lines 45-53, and col. 65, line 1, through col. 108, line 50.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a group I-S1 subtilase or group I-S2 subtilase variant comprising any of the **R**(45)[44]**H**, **K**(94)[92]**N**, and **E**(271)[265]**A** substitutions taught by Poulose et al. '937 in order to provide net charge-modified variants suitable for incorporation in detergent compositions that produce diverse pH ranges when dissolved in wash liquor, and that further comprises one of the **N**(62)[61]**S/Q/D/E/P** substitutions that each of the four patents to Brode et al. relied on herein teach will improve wash performance, as well as to prepare a detergent composition comprising such a variant subtilase as well as cellulases, lipases, and amylases. This is because Poulose et al. '937 teach that their net charge-altering substitutions contribute to maintaining the bulk properties of the modified subtilase within a determinable pH range and because Brode et al. teach that their amino acid substitutions, wherein modified positions may have a more negative charge as a result, advantageously modify subtilases to improve their wash performance. Such an artisan would have had a reasonable expectation of success in preparing a subtilisin variant having worthwhile bulk properties within a determinable pH range as well as improved was performance by introducing one or more of the **R**(45)[44]**H**, **K**(94)[92]**N**, and **E**(271)[265]**A** substitutions taught by Poulose et al. '937 when further combining an **N**(62)[61]**S/Q/D/E/P** substitution of any of Brode et al. and in preparing detergent compositions comprising such variants and other enzymes, according to claims 16, 18, 24, 29, 46, and 50-54 herein where substitutions taught by Brode et al. may also alter the net molecular charge. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

H. Claims 16, 18, 20, 21, 25, 41, 50, and 52-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any among Brode et al. US 6,436,690, US 6,455,295, US 6,475,765, or US 6,599,730, discussed above, in view of Kettling et al. **US 2003/0157645**, made of record herewith.

The teachings of Brode et al. '765, '690, '295, or '730, discussed above, are taken as before.

Kettling et al. are available as prior art herein under 35 U.S.C. § 102(a) and (e) in view of their teachings at pages 10-12 of their 21 December 2001-filed US priority application No. 60/343,056 of the preparation of variants of a group I-S1 subtilase, the subtilisin E endogenous to *Bacillus subtilis* having one or more of the **S**(9)[9]**R**, **P**(14)[14]**T**, **V**(51)[50]**I**, and **A**(228)[222]**T** substitutions and further teach that these substitutions provide subtilase variants having one or more improved characteristics in laundry detergents, as well as the preparation of detergent compositions comprising the subtilisin E variants. See Figure 2, SEQ ID NO:2, and paragraphs 0059-0116 of the '645 publication.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a group I-S1 subtilase variant comprising any of the **S**(9)[9]**R**, **P**(14)[14]**T**, **V**(51)[50]**I**, and **A**(228)[222]**T** substitutions taught by Kettling et al. in order to variants having one or more improved characteristics in laundry detergents, and that further comprises one of the **N**(62)[61]**S/Q/D/E/P** substitutions that each of the four patents to Brode et al. relied on herein teach will improve wash performance, as well as to prepare a detergent composition comprising such a variant subtilase as well as cellulases, lipases, and amylases. This is because Kettling et al. teach that amino acid substitutions in the amino acid sequence of a group I-S1 subtilase improve its efficiency in detergent compositions and because Brode et al. teach that their amino acid substitutions advantageously modify subtilases to improve their wash performance. Such an artisan would have had a reasonable expectation of success in preparing a subtilisin variant having improved was performance by introducing one or more of the **S**(9)[9]**R**, **P**(14)[14]**T**, **V**(51)[50]**I**, and **A**(228)[222]**T** substitutions taught by Kettling et al. and further combining an **N**(62)[61]**S/Q/D/E/P** substitution of any of Brode et al. ,and in preparing detergent compositions comprising such variants and other enzymes, according to claims 16, 18, 20, 21, 25, 41, 50, and 52-54 herein where substitutions taught by Brode et al. also improve wash performance of a subtilase variant. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

I. Claims 16, 18, 23, 24, 28, 29, 35, 36, 38, 39, and 50-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any among Brode et al. US 6,436,690, US 6,455,295, US 6,475,765, or US 6,599,730, discussed above, in view of Estell et al. **US 7,332,320**, made of record herewith.

The teachings of Brode et al. '765, '690, '295, or '730, discussed above, are taken as before.

Estell et al. are available as prior art under 35 U.S.C. § 102(a) and (e) in view of the teachings of preparation of subtilase group I-S1 and I-S2 variants having one or more of the substitutions **V**(28)[28]**I**, **V**(30)[30]**I**, **I**(35)[35]**T**, **I**(35)[35]**V**, **A**(88)[86]**T**, **K**(94)[92]**N**, **G**(160)[158]**A**, **S**(163)[159]**G**, **S**(163)[159]**N**, **S**(163)[159]**A**, **Y**(167)[161]**K**, **Y**(171)[165]**C**, **R**(186)[180]**L**, **R**(186)[180]**H**, **S**(188)[182]**G**, **S**(190)[184]**A**, and **Y**(192)[186]**H** at pages 35-39 of their 31 December 2001-filed US provisional application 60/344,702. Estell et al. teach the preparation of variants of group I-S1 and group I-S2 subtilases, the subtilisins BPN' ands 309, having reduced immunogenicity conferred by the above substitutions disclosed in their priority document for incorporation in laundry detergents, as well as the preparation of detergent compositions that comprise such subtilase variants and "other . . . proteases, amylases, cellulases, lipases or endoglycosidases". See cols. 16-19 and the teaching from line 4 at col. 27 through line 27 at col. 31.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a group I-S1 or group I-S2 subtilase variant comprising any of the **V**(28)[28]**I**, **V**(30)[30]**I**, **I**(35)[35]**T**, **I**(35)[35]**V**, **A**(88)[86]**T**, **K**(94)[92]**N**, **G**(160)[158]**A**, **S**(163)[159]**G**, **S**(163)[159]**N**, **S**(163)[159]**A**, **Y**(167)[161]**K**, **Y**(171)[165]**C**, **R**(186)[180]**L**, **R**(186)[180]**H**, **S**(188)[182]**G**, **S**(190)[184]**A**, substitutions taught by Estell et al. to reduce immunogenicity and that further comprises one of the **N**(62)[61]**S/Q/D/E/P** substitutions that each of the four patents to Brode et al. relied on herein teach will improve wash performance, as well as to prepare a detergent composition comprising such a variant subtilase as well as cellulases, lipases, and amylases. This is because Estell et al. teach that introducing their amino acid substitutions in the amino acid sequences of group I-S1 and group I-S2 subtilases reduce their immunogenicity and because Brode et al. teach that their amino acid substitutions advantageously modify subtilases to improve their wash performance. Such an artisan would have had a reasonable expectation of success in preparing a subtilisin variant having reduced immunogenicity and improved wash performance by introducing one or more of the **V**(28)[28]**I**, **V**(30)[30]**I**, **I**(35)[35]**T**, **I**(35)[35]**V**, **A**(88)[86]**T**, **K**(94)[92]**N**, **G**(160)[158]**A**, **S**(163)[159]**G**, **S**(163)[159]**N**, **S**(163)[159]**A**, **Y**(167)[161]**K**, **Y**(171)[165]**C**, **R**(186)[180]**L**, **R**(186)[180]**H**, **S**(188)[182]**G**, **S**(190)[184]**A**, and **Y**(192)[186]**H** substitutions taught by Estell et al. and further combining an **N**(62)[61]**S/Q/D/E/P** substitution of any of Brode et al. and in preparing detergent compositions comprising such variants and other enzymes, according to claims 16, 18, 23, 24, 28, 29, 35, 36, 38, 39, and 50-54 herein where the subtilisin BPN'-correspondent position 62 is not taught by any of Brode et al. to influence immunogenicity and the substitutions taught by Brode et al. also improve wash performance of a subtilase variant. Based upon the teachings of the cited references, the level

of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

J. Claims 16, 18-28, 30, 32-40, 42-47, and 50-54 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any among Brode et al. US 6,436,690, US 6,455,295, US 6,475,765, or US 6,599,730, discussed above, in view of Roggen et al. **US 2005/0181446**, made of record herewith.

The teachings of Brode et al. '765, '690, '295, or '730, discussed above, unique are taken as before.

The Pre-Grant Publication of Roggen et al. '446 is first available as prior art under 35 U.S.C. § 102(b) in view of the 21 March 2001 filing date of its priority US provisional application 60/277,817 wherein Roggen et al. teach the preparation of group I-S1 and group I-S2 subtilases having one or more immunogenicity-modifying substitutions generically based on the numbering of the subtilisin BPN' amino acid sequence in an alignment that spans pages 104 through 106 of the '817 provisional application of the amino acid sequences of subtilisins 309 and BPN', as well as the subtilisin PD498. In the alignment of the provisional application, the relative absences of amino acids that occur within the subtilisin 309 amino acid sequence relative to the subtilisin BPN' amino acid sequence are assigned at the subtilisin BPN'-correspondent positions 36, 56, 159, and 164-166. A generic amino acid, rendered only by position number in claims 35-38[1] of the provisional application, is for the purposes of this rejection, assigned the amino acid residing in the subtilisin 309 amino acid sequence at the subtilisin BPN'-correspondent position, thus claims 35-38 therein teach the introduction of immunogenicity-modifying substitutions including **Q**(2)[2]**L**, **I**(8)[8]**T**, **A**(15)[15]**T**, **A**(15)[15]**M**, **A**(16)[16]**P**, **N**(18)[18]**H**, **R**(19)[19]**F**, **R**(19)[19]**G**, **R**(19)[19]**I**, **R**(19)[19]**K**, **R**(19)[19]**L**, **R**(19)[19]**W**, **L**(21)[21]**F**, **T**(22)[22]**S**, **T**(22)[22]**A**, **T**(22)[22]**L**, **T**(22)[22]**G**, **G**(23)[23]**S**, **S**(24)[24]**P**, **I**(35)[35]**T**, **I**(35)[35]**V**, **T**(38)[37]**S**, **P**(40)[39]**L**, **R**(45)[44]**H**, **L**(75)[73]**I**, **V**(81)[79]**A**, **A**(88)[86]**T**, **E**(89)[87]**G**, **A**(108)[106]**V**, **A**(108)[106]**T**, **L**(111)[108]**I**, **L**(111)[108]**V**, **V**(139)[137]**L**, **V**(139)[137]**I**, **S**(144)[142]**D**, **S**(144)[142]**N**, **S**(144)[142]**P**, **R**(145)[142]**G**, **A**(151)[149]**V**, **A**(151)[149]**G**, **S**(163)[160]**G**, **S**(163)[160]**N**, **S**(163)[160]**A**, **A**(168)[162]**G**, **A**(169)[163]**G**, **A**(172)[166]**V**, **R**(186)[180]**H**, **R**(186)[180]**L**, **S**(188)[182]**G**, **S**(190)[180]**A**, **Y**(192)[186]**H**, **V**(203)[197]**F**, **V**(203)[197]**S**, **T**(213)[207]**A**, **V**(234)[228]**I**, **S**(240)[234]**F**, **S**(242)[236]**T**, **A**(254)[248]**S**, **S**(265)[259]**G**, **S**(265)[257]**T**, **V**(268)[26L]**L**, **V**(268)[262]**I**, **N**(269)[263]**K**, **N**(269)[263]**T**, and **E**(271)[263]**A**, wherein resulting group I-S1 and

[1] Claims 39-40 of the provisional application recite amino acid positions common to subtilisin BPN'-correspondent positions but add positions exclusive to the PD498 amino acid sequence.

I-S2 subtilase variants may advantageously be incorporated in detergent compositions that may further comprise other enzymes, including "proteases, amylases, lipolytic enzymes, cutinases, cellulases, peroxidases, [and] oxidases". See pages 6, 62, and 63.

The Pre-Grant Publication of Roggen et al. '446 is additionally available as prior art under 35 U.S.C. § 102(b) in view of the 21 September 2001-filed US application 09/957,806 which became the '446 publication of Roggen et al., wherein claims 78, 79, and 82 further teach several more immunogenicity-modifying substitutions, including **S**(9)[9]**L**, **S**(9)[9]**V**, **S**(9)[9]**R**, **S**(9)[9]**G**, **P**(14)[14]**T**, **P**(14)[14]**M**, **P**(14)[14]**V**, **P**(14)[14]**Q**, **P**(14)[14]**L**, **P**(14)[14]**H**, **P**(14)[14]**R**, **P**(14)[14]**I**, **G**(20)[20]*, **F**(50)[49]**S** **V**(51)[50]**I**, **P**(55)[54]**A**, **S**(128)[126]**I**, **Q**(137)[135]**H**, **A**(158)[156]**V**, **A**(158)[156]**L**, **A**(158)[156]**M**, **Y**(167)[161]**K**, **S**(212)[206]**L**, **T**(255)[249]**A**, **S**(256)[250]**G**, **L**(257)[251]**G**, **G**(258)[256]**K**, **S**(259)[253]**A**, **S**(259)[253]**N**, **L**(262)[256]**Q**, and **L**(262)[256]**V**. Group I-S2 subtilase variants comprising one or more of these substitutions may advantageously be incorporated in detergent compositions that may further comprise other enzymes, including "proteases, amylases, lipolytic enzymes, cutinases, cellulases, peroxidases, [and] oxidases". See paragraphs 0025 and 0239-0242.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a group I-S1 or group I-S2 subtilase variant comprising any of the immunogenicity-modifying amino acid substitutions **Q2L**, **I8T**, **S9L/V/R/G**, **P14T/M/V/Q/L/H/R/I**, **A15T/M**, **A16P**, **N18H**, **R19F/G/I/K/L/W**, **G20***, **L21F**, **T22S/A/L/G**, **G23S**, **S24P**, **I35T/V**, **T**(38)[37]**S**, **P**(40)[39]**L**, **R**(45)[44]**H**, **F**(50)[49]**S**, **V**(51)[50]**I**, **L**(75)[73]**I**, **V**(81)[79]**A**, **A**(88)[86]**T**, **E**(89)[87]**G**, **A**(108)[106]**V/T**, **L**(111)[108]**I/V**, **S**(128)[126]**I**, **Q**(137)[135]**H**, **V**(139)[137]**L/I**, **S**(144)[142]**D/N/P**, **R**(145)[143]**G**, **A**(151)[149]**V/G**, **A**(158)[156]**V/L/M**, **S**(163)[160]**G/N/A**, **Y**(167)[161]**K**, **A**(168)[162]**G**, **A**(169)[163]**G**, **A**(172)[166]**V**, **R**(186)[180]**H/L/G**, **S**(190)[180]**A**, **Y**(192)[186]**H**, **V**(203)[197]**F/S**, **S**(212)[206]**L**, **T**(213)[207]**A**, **V**(234)[228]**I**, **S**(240)[234]**F**, **S**(242)[236]**T**, **A**(254)[248]**S**, **T**(255)[249]**A**, **S**(256)[250]**G**, **L**(257)[251]**G**, **G**(258)[256]**K**, **S**(259)[253]**A/N**, **L**(262)[256]**Q/V**, **S**(265)[259]**G/T**, **V**(268)[26L]**L/I**, **N**(269)[263]**K/T**, and **E**(271)[263]**A** taught by Roggen et al. in preparing a variant I-S1 of I-S2 subtilase and to further combine that substitution with one of the **N**(62)[61]**S/Q/D/E/P** substitutions that each of the four patents to Brode et al. relied on herein teach will improve wash performance, as well as to prepare a detergent composition comprising such a variant subtilase as well as cellulases, lipases, and amylases. This is because Roggen et al. teach that introducing their amino acid substitutions in the amino acid sequences of group I-S1 and group I-S2 subtilases can modify the immunogenicity of the subtilase and because Brode et al. teach that their amino acid

substitutions advantageously modify subtilases to improve their wash performance. Such an artisan would have had a reasonable expectation of success in preparing a subtilisin variant having modified immunogenicity and improved wash performance by introducing one or more of the several substitutions taught by Roggen et al. and further combining an **N**(62)[61]**S/Q/D/E/P** substitution of any of Brode et al., as well as preparing detergent compositions comprising such variants and other enzymes, according to claims 16, 18-28, 30, 32-40, 42-47, and 50-54 herein, such as the following substitution sets of claim 47:

Q2L+N62D, S3L+N62D+S163A+S190A, S3T+P14Q+A15M+R19K+N62D+S144D, I35T+N62D, N62D+R145G, N62D+A151G, N62D+S265G, and S9R+A15T+T22A+ N62D.

This is because the subtilisin BPN'-correspondent position 62 is not taught by either of Roggen et al. or Brode et al. to influence immunogenicity and the substitutions taught by Brode et al. also improve wash performance of a subtilase variant. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims are allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Jon. P. Weber, Ph.D., can be reached at 571.272.0925. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

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